IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of :

Serial No. 09/380,059 : Group Art Unit 1614

Filed August 25, 1999 :

For: PHARMACEUTICAL COMPOSITION

DECLARATION UNDER RULE 132

I, Hiroyuki ODAKA, a citizen of Japan, residing at 12-12, Katsuragi 2-chome, Kita-ku, Kobe, HYOGO, Japan, declare:

That, I was born on December 9, 1955 in Hiroshima, Japan;

That, I graduated with a bachelor degree from the Department of Agriculture, Tohoku University, Japan, on March 1977;

That, I was awarded an Agricultural doctoral degree from Tohoku University, Japan, on February 1991 on a doctoral thesis entitled "Study on environmental factors affecting on the development of noninsulin-dependent diabetes mellitus";

That, I have been an employee of Takeda Chemical Industries, Ltd., Osaka Japan since April, 1979;

That, I have been engaged in research work in the field of pharmacology and physiology on diabetes mellitus and hyperlipidemia;

That, I am a Research Manager of Pharmaceutical Research Laboratories 2, Pharmaceutical Research Division of said company;

That, I am a member of Japanese Diabetes Society;

That, I am a co-inventor of the invention claimed in U.S. Patent Application Serial No. 09/380,059;

That, the following Experiment was carried out by technicians under my direct guidance and supervision;

Experiment

Wistar fatty rats (15 weeks old, male), a model of obesity

and type 2 diabetes mellitus, were divided into Groups A to D.

To Group A (5 rats), a 0. 5% (w/w) methylcellulose/physiological saline suspension (2 ml/kg body weight/day) was orally administered for 28 days. This group was a control group.

To Group B (5 rats), a 0. 5% (w/w) methylcellulose/ physiological saline suspension (2 ml/kg body weight/day) containing pioglitazone hydrochloride (0.3 mg/kg body weight/day) was orally administered for 28 days.

To Group C (6 rats), a 0. 5% (w/w) methylcellulose/ physiological saline suspension (2 ml/kg body weight/day) containing sibutramine (3 mg/kg body weight/day) was orally administered for 28 days.

To Group D (5 rats), a 0. 5% (w/w) methylcellulose/ physiological saline suspension (2 ml/kg body weight/day) containing pioglitazone hydrochloride (0.3 mg/kg body weight/day) and a 0. 5% (w/w) methylcellulose/ physiological saline suspension (2 ml/kg body weight/day) containing sibutramine (3 mg/kg body weight/day) were orally administered for 28 days.

During administration for 28 days, the rats were allowed to take food freely.

Before and after the administration for 28 days, body weights of the rats were determined, and blood was collected from the tail vein of the rats. The results of the body weight increase are shown in Table 2.

The HbA1c level in the blood of the subjects was determined using an autoanalysing system (HLC-723GHbV, Tosoh, Japan). After separating plasma from the blood, glucose and triglyceride in the plasma were quantified using an autoanalysing system (7070, Hitachi Corporation, Japan). Changes in HbA1c level, plasma glucose and plasma triglyceride are shown in Table 1.

In the following tables, "pio", "sib" and "HbA1c" mean

pioglitazone hydrochloride, sibutramine and glycosylated hemoglobin, respectively. Figures in the tables represent mean ± SD (standard deviation).

Table 1

	HbA1 c(%)	Plasma glucose (mg/dl)	Plasma triglyceride (mg/dl)
Group A(Control)	0.1±0.5	37.8± 75.5	164.7± 52.2
Group B(pio)	- 0.3±0.3	- 0.3± 60.7	78.7±102.9
Group C(sib)	- 0.2±0.5	- 83.2± 48.3	- 36.2± 94.3
Group D(pio+sib)	- 1.2±0.4	-101.4± 55.2	- 67.3±106.9

Table 2

	Body weight increase (g)
Group A(Control)	85.4±10.8
Group B(pio)	108.4±14.8
Group C(sib)	82.0±16.8
Group D(pio+sib)	70.8± 8.3

As can be seen from the resulting data as shown in Table 1, use of pioglitazone hydrochloride in combination with sibutramine provided unexpectedly superior effects of lowering HbA1c, plasma glucose and plasma triglyceride.

Further, as shown in Table 2, use of pioglitazone hydrochloride in combination with sibutramine unexpectedly provided an effect of inhibiting body weight increase.

That, it is my opinion that the Experiments described above demonstrating the use of pioglitazone hydrochloride in combination with sibutramine, clearly show unexpected results.

I, the undersigned, declare further that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signed this 20th day of August, 2001;

Hiroyuki Odaka

Hiroyuki ODAKA